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Pasteurella multocida and *Bordetella bronchiseptica* Infections in Rabbits

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The natural history of infection with *Pasteurella multocida* and *Bordetella bronchiseptica* in domestic rabbits was studied prospectively at a commercial rabbitry. At weaning, about 25% of rabbits had nasal infections with *P. multocida* and 75% had infections with *B. bronchiseptica*. Infection of weanling rabbits paralleled nasal infections of their dams. The proportion of rabbits with both infections increased with age. At 2 to 4 months old, about 50% of rabbits with *P. multocida* or *P. multocida* and *B. bronchiseptica* infections had upper respiratory disease (URD), whereas rabbits with *B. bronchiseptica* infection had no disease. In rabbits about 10 months old, 75% with *P. multocida* or *P. multocida* and *B. bronchiseptica* infections had URD, whereas virtually none with *B. bronchiseptica* infection had disease. Disease of the nares, paranasal sinuses, middle ears, and lungs was associated with *P. multocida* and not *B. bronchiseptica* infection. In adult rabbits with nasal *P. multocida* infection, with or without signs of URD, about 80% had concurrent infection of the paranasal sinuses and middle ears and 20% had infection of the bronchi and lungs. In rabbits without nasal *P. multocida* infection, 20 to 35% had *P. multocida* infection of the paranasal sinuses and middle ears. Weanling rabbits with and without *P. multocida* infection had similar immunoglobulin G (IgG) levels. In rabbits observed prospectively, the only antibody differences between those transiently and persistently infected with *P. multocida* were a diminished IgA response in nasal lavages and an earlier IgM response in sera of transiently infected rabbits. IgG levels increased with the duration of infection. There was no relationship between immunoglobulin levels and freedom from *P. multocida* infection.

Pasteurella multocida, the most common respiratory pathogen of rabbits, is usually associated with upper respiratory disease (URD), characterized by rhinitis with mucopurulent nasal discharge, and less commonly with otitis media, conjunctivitis, pneumonia, abscesses, genital infections, and septicemia (10). While *Bordetella bronchiseptica* is a recognized respiratory pathogen in guinea pigs, dogs, and pigs, its significance in rabbits has not been established. Natural infections with *B. bronchiseptica* were common in healthy rabbits (28, 29). Both *P. multocida* and *B. bronchiseptica* were common in the respiratory tracts of healthy and diseased rabbits (8, 16, 27). To determine the relative significance of these organisms, we studied the natural history of *P. multocida* and *B. bronchiseptica* infections in a commercial rabbitry in which both organisms were endemic (4). We determined infection rates of *P. multocida* and *B. bronchiseptica*, sites of predilection, and association with respiratory tract diseases. Additionally, the humoral immune response to *P. multocida* in relation to infection was observed prospectively.

MATERIALS AND METHODS

Rabbitry. The study was conducted at a commercial rabbitry which sold rabbits (fryers) for market. Nasal cultures from 42 adult breeders revealed that 31% were infected with *P. multocida* before the study. A field trial of a live streptomycin-dependent *P. multocida* vaccine was conducted at the rabbitry (4). Since no protection against pasteurellosis was afforded by the vaccine, the natural history of infection in the colony was studied. Rabbits were New Zealand White, California, or hybrids. They were maintained in an aluminum-sided shed in hanging wire cages. Water was supplied by an automatic watering system, and feed was provided once daily. Rabbits were weaned at 5 to 6 weeks of age, and the sexes were segregated into groups of six to eight rabbits per cage. Most bucks and some does were marketed at 9 to 11 weeks old. The majority of does were housed individually and added to the breeding colony. Does were initially bred at about 6 months and rebred when litters were weaned.

In litters with URD, in the doe and two preweanlings, 4 to 6 weeks of age, deep nasal culture was used to obtain samples for detection of *P. multocida* and *B. bronchiseptica* infections. Two weanling does from litters without signs of URD were randomly selected for long-term study of *P. multocida* and *B. bronchiseptica* infections and immunoglobulin responses in sera and nasal lavages to *P. multocida*. Samples were obtained from the two does at weaning and 1, 2, 3, and ≥6 months after weaning. Does were >6 months old when necropsied; the mean age was 10.2 months. Clinical signs of URD were a mucopurulent exudate from the nares and matted forepaws. Disease at necropsy was defined as the presence of mucopurulent or purulent exudate associated with inflammation at the site. Based on *P. multocida* culture results, rabbits which were observed from weaning to necropsy were divided into groups for analysis of immunoglobulins to *P. multocida*. The groups of rabbits were noninfected (group 1), infected at weaning and still infected at necropsy (preweaning infection) (group 2), infected 1 month after weaning and at necropsy (early postweaning infection) (group 3), infected 2 months after weaning and at necropsy (late postweaning infection) (group 4) and infected 1 or 2 months after weaning but cleared of infection by necropsy (transient postweaning infection) (group 5).

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TABLE 1. Relationship of nasal infections in does and preweanlings with URD

Bacterium	Does (n = 31)		Preweanlings[a] (n = 62)	
	Status	No. (%)	No. positive (%)	No. negative (%)
P. multocida	Positive	19 (61.3)	26 (41.8)	12 (19.4)
	Negative	12 (38.7)	12 (19.4)	12 (19.4)
B. bronchiseptica	Positive	25 (80.6)	43 (69.4)	7 (11.3)
	Negative	6 (19.4)	6 (9.6)	6 (9.7)

[a] Preweanlings were 4 to 6 weeks of age and with the doe.

Collection of samples. Rabbits >2 months old were sedated with ketamine hydrochloride (30 mg/kg) (Parke, Davis & Co., Morris Plains, N.J.) and acepromazine maleate (0.01 mg/kg) (Fort Dodge Laboratories, Inc., Fort Dodge, Iowa) intramuscularly for collection of samples. Blood was obtained from the auricular artery; serum was removed and stored at −20°C. Nasal lavages were obtained by infusing 0.5 to 1 ml of sterile phosphate-buffered saline into the nares and collecting drops which were sneezed onto a sterile petri dish. The fluid was collected and stored at −20°C. The remaining fluid was collected on a type 4 Calgiswab (Spectrum Laboratories, Inc., Los Angeles, Calif.) which was inoculated directly onto sheep blood agar plates. At necropsy, the nares, paranasal sinuses, middle ears, and terminal bronchi were examined and swabbed with type 4 Calgiswabs which were inoculated onto blood agar plates.

Serology. Sera diluted 1:100 were tested by enzyme immunoassay for immunoglobulin M (IgM) and IgG antibodies against *P. multocida* (5, 15). Nasal lavages diluted 1:10 were similarly tested for IgA antibodies (5). Peroxidase-conjugated goat anti-rabbit IgG (Kirkegaard and Perry Laboratories, Inc., Gaithersburg, Md.) was used at 1:3,200; goat anti-rabbit IgM (Organon Teknika, Malvern, Pa.) was used at 1:2,000; and goat anti-rabbit IgA (Organon Teknika) was used at 1:3,000. Positive control sera and lavages were from rabbits experimentally infected with *P. multocida*; control IgG optical density (OD) averaged 1.5; IgM OD averaged 0.5; and IgA OD averaged 0.8. Negative control sera and lavages were from our own *Pasteurella*-free rabbit colony; ODs were <0.2 for IgG and IgM and <0.05 for IgA. A_{490}s were determined on a BioTek EIA reader model EL308. ODs of >0.3 were considered positive for IgM and IgG; ODs of >0.1 were positive for IgA.

Bacteriology. Blood agar plates were examined after 2 days of incubation at 37°C with 5% CO_2. Isolates were identified as *P. multocida* or *B. bronchiseptica* based on cultural and biochemical characteristics (26).

Statistical analysis. Differences in infection rates were tested for significance ($P < 0.05$) by chi-square analysis. Immunoglobulin levels were compared by a pooled-variance t test.

RESULTS

Bacterial isolation and disease. Among preweanling rabbits with URD, those with *P. multocida* or *B. bronchiseptica* infection were more likely to have a dam with the same infection (Table 1). Of 192 weanling rabbits without URD, 43 (22.4%) had nasal *P. multocida* infection, whereas 141 (73.5%) had *B. bronchiseptica* infection (Table 2). Over the next 2 months, the proportion of rabbits with both *P. multocida* and *B. bronchiseptica* infections increased. Two months after weaning, about 50% of rabbits with *P. multocida* or *P. multocida* and *B. bronchiseptica* infections had URD, whereas rabbits with *B. bronchiseptica* infection or neither infection had virtually no signs of URD (Table 3). This difference was statistically significant ($P < 0.001$).

TABLE 2. Nasal infection with *P. multocida* and *B. bronchiseptica* in female rabbits

Bacterium	No. (%) of rabbits with nasal infection by age (wk)		
	5–6	9–10	13–14
P. multocida	11 (5.7)	17 (11.6)	8 (6.0)
B. bronchiseptica	109 (56.8)	61 (41.5)	56 (42.1)
P. multocida and *B. bronchiseptica*	32 (16.7)	56 (38.1)	60 (45.1)
Neither	40 (20.8)	13 (8.8)	9 (6.8)
Total	192 (100)	147 (100)	133 (100)

In 95 adult female rabbits examined at necropsy, *P. multocida* was more frequently isolated from the paranasal sinuses and middle ears (Table 4). Isolation of *P. multocida* from each of the respiratory sites was strongly associated with disease, while isolation of *B. bronchiseptica* only was rarely associated with disease. The difference for each of the four sites was statistically significant ($P < 0.001$). Rabbits infected with *P. multocida* and *B. bronchiseptica* had a pattern of disease occurrence intermediate between that for rabbits infected with *P. multocida* or *B. bronchiseptica*. Among the 54 rabbits with *P. multocida*-associated rhinitis, 6 (11%) were unilateral; among the 47 rabbits with *P. multocida*-associated sinusitis, 8 (17%) were unilateral; and among the 46 rabbits with otitis media, 14 (30%) were unilateral. While there was an increasing trend in mean age for rabbits with *B. bronchiseptica* (9.6 months), *B. bronchiseptica* and *P. multocida* (10.1 months), and *P. multocida* (10.8 months) infections, the differences were not statistically significant ($P > 0.05$). Rabbits with *P. multocida* infection of the nares often had concurrent infection of the paranasal sinuses and middle ears (Table 5). However, infection was detected in other respiratory sites in 4 to 35% of rabbits which did not have nasal *P. multocida* infection.

TABLE 3. Nasal infection and URD in female rabbits

Bacterium	No. (% distribution) of rabbits with nasal infection by age (wk)	
	9–10	13–14
P. multocida		
Normal	7 (41.2)	4 (50.0)
URD	10 (58.8)	4 (50.0)
B. bronchiseptica		
Normal	38 (62.3)	53 (94.6)[a]
URD	23 (37.7)	3 (5.4)
P. multocida and *B. bronchiseptica*		
Normal	25 (44.6)	31 (51.7)
URD	31 (55.4)	29 (48.3)
Neither		
Normal	10 (76.9)	9 (100.0)
URD	3 (23.1)	0 (0)

[a] URD significantly ($P < 0.001$) lower than in rabbits with *P. multocida* or *P. multocida* and *B. bronchiseptica* infections.

TABLE 4. Respiratory infection and disease in adult female rabbits at necropsy

Bacterium	Nares		Paranasal sinuses		Middle ears		Bronchi and lungs	
	Infection[a]	Disease[b]	Infection	Disease	Infection	Disease	Infection	Disease
P. multocida	24	21 (87.5)	44	37 (84.1)	53	45 (84.9)	7	7 (100)
B. bronchiseptica	24	2 (8.3)[c]	21	1 (4.8)[c]	12	0 (0)[c]	66	0 (0)[c]
P. multocida and *B. bronchiseptica*	45	33 (73.3)	21	10 (47.6)	11	1 (9.1)	8	5 (62.5)
Neither	2	0 (0)	9	0 (0)	19	0 (0)	14	2 (14.3)

[a] Number rabbits infected.
[b] Number (%) of rabbits with disease.
[c] Disease significantly ($P < 0.001$) lower than in rabbits with *P. multocida* infection.

Nine rabbits (11.5%) with no clinical signs of disease and with negative nasal cultures had infection of the middle ears. Among the 78 adult rabbits with *P. multocida* infection in at least 1 of the respiratory sites sampled, 69 (88.5%) had nasal infection but only 40 (51.3%) showed antemortem signs of URD (Table 6). Regardless of the presence of URD, the proportion of rabbits with infection at other respiratory sites was similar.

Antibody responses to *P. multocida*. Since isolation of *B. bronchiseptica* was not associated with disease in rabbits of any age, sera were tested for antibodies to *P. multocida* only. A comparison of IgM and IgG levels in weanling rabbits with and without *P. multocida* infection revealed no significant ($P > 0.05$) differences in either mean immunoglobulin levels or proportion of rabbits with absorbance values greater than 0.30 (Fig. 1). Mean IgM and IgG levels for 35 culture-negative rabbits were 0.214 (standard deviation = 0.098) and 0.259 (standard deviation = 0.350), respectively, whereas the corresponding values for 35 culture-positive rabbits were 0.247 (standard deviation = 0.094) and 0.372 (standard deviation = 0.395), respectively.

Rabbits from which samples were obtained culturally and serologically from weaning to maturity were divided into five groups on the basis of their acquisition of *P. multocida* infection (Table 7). The groups were noninfected (group 1), preweaning infection (group 2), early postweaning infection (group 3), late postweaning infection (group 4), and transient postweaning infection (group 5). The mean ages of rabbits at necropsy in the groups ranged from 9.0 to 10.4 months and were not significantly ($P > 0.05$) different. Only one of five noninfected rabbits had IgG antibodies at weaning; IgG antibodies in this rabbit were undetectable 1 month later. Eighty percent of noninfected rabbits developed IgM antibodies which persisted into adulthood. About 40% of rabbits which acquired *P. multocida* infection before weaning had IgG antibodies at weaning. In this group, the proportions of rabbits with IgA, IgM, and IgG antibodies increased at successive testings. A similar pattern of increasing proportion of rabbits with IgA, IgM, and IgG antibodies was observed in rabbits that acquired infection 1 month after weaning. A delayed response was observed in rabbits that acquired infection 2 months after weaning. The group with transient infection had a diminished number of rabbits with IgA antibodies. IgA antibodies were diminished in adult rabbits which were noninfected and transiently infected compared with rabbits with persistent infections. However, in all groups, the proportion of rabbits with IgM and IgG at maturity was similar. The mean absorbance levels of antibodies were compared in the five groups (Fig. 2). Rabbits that acquired infection before (group 2) or soon after (group 3) weaning developed the highest IgG antibody titers. Those which acquired infection 2 months after weaning (group 4) had lower mean IgG antibodies, whereas noninfected rabbits (group 1) had the lowest mean IgG antibody levels. Mean IgM antibody levels were similar in all groups of rabbits and remained elevated.

DISCUSSION

In this study, rabbits in a commercial colony were monitored prospectively for acquisition of *P. multocida* and *B. bronchiseptica* infections. As rabbits aged, infection with *P. multocida* and *B. bronchiseptica*, particularly combined infections, increased. Signs of URD also increased with age. URD was significantly associated with *P. multocida* infection or combined *P. multocida* and *B. bronchiseptica* infections but not *B. bronchiseptica* infection alone. In adult rabbits, *P. multocida* was most frequently isolated, in decreasing order, from the middle ears, paranasal sinuses, and nares, while *B. bronchiseptica* was most frequently isolated from the bronchi, nares, and paranasal sinuses. Infection with *P. multocida* correlated with inflammation and mucopurulent or purulent exudation, whereas infection with *B. bronchiseptica* was not significantly associated with disease in respiratory sites. In the absence of URD, subclinical infection with *P. multocida* occurred in about 25% of rabbits 5 to 14 weeks old and 40% of adult rabbits. In adult rabbits, 5% had infection of the middle ears or paranasal sinuses only without signs of URD.

While the prevalence of *P. multocida* and *B. bronchiseptica* infections within age groups may vary between rabbit colonies, it consistently increases with age. Nakagawa et al.

TABLE 5. Relationship of nasal infection with *P. multocida* and infection at other respiratory sites in adult female rabbits

Nares infection	No.	No. (%) of rabbits with infection		
		Paranasal sinuses	Middle ears	Bronchi and lungs
Yes	69	60 (87.0)	55 (79.7)	14 (20.3)
No	26	5 (19.2)	9 (34.6)	1 (3.8)
Total	95	65 (68.4)	64 (67.4)	15 (15.8)

TABLE 6. Association of *P. multocida* infection with clinical signs in adult female rabbits

URD	No.	No. (%) of rabbits with infection			
		Nares	Paranasal sinuses	Middle ears	Bronchi and lungs
Present	40	40 (100)	38 (95.0)	33 (82.5)	8 (20.0)
Absent	38	29 (76.3)	27 (71.1)	31 (81.6)	7 (18.4)
Total	78	69 (88.5)	65 (83.3)	64 (82.1)	15 (19.2)

TABLE 7. Infection with and antibodies to *P. multocida* in female rabbits from weaning to maturity

Group	No.	Proportion of rabbits with antibodies by mo after weaning:											
		0			1			2			≥6		
		IgA	IgM	IgG	IgA	IgM	IgG	IgA	IgM	IgG	IgA	IgM	IgG
Noninfected[a]	5	0	0	20	20	80	0	20	80	0	20	100	80
Preweaning infection[b]	14	0	0	43	17[f]	50[f]	33[f]	57	71	79	57	93	93
Early postweaning infection[c]	21	0	0	24	14[f]	60	40[f]	35[f]	85[f]	70[f]	50	90[f]	95
Late postweaning infection[d]	29	0	0	14[f]	13	36[f]	18[f]	15[f]	57[f]	25	54	97[f]	97
Transient postweaning infection[e]	8	0	13	38	0	25	13	0	38	13	38	100	100
Total	77	0	4	25	13	47	25	27	67	44	49	95	95

[a] Infection never detected.
[b] Infected at weaning and throughout life.
[c] Infection was detected 1 month after weaning and throughout life.
[d] Infection was detected 2 months after weaning and throughout life.
[e] Infection was detected at 1 or 2 months after weaning but not at necropsy.
[f] One to five fewer samples than number indicated were available for testing.

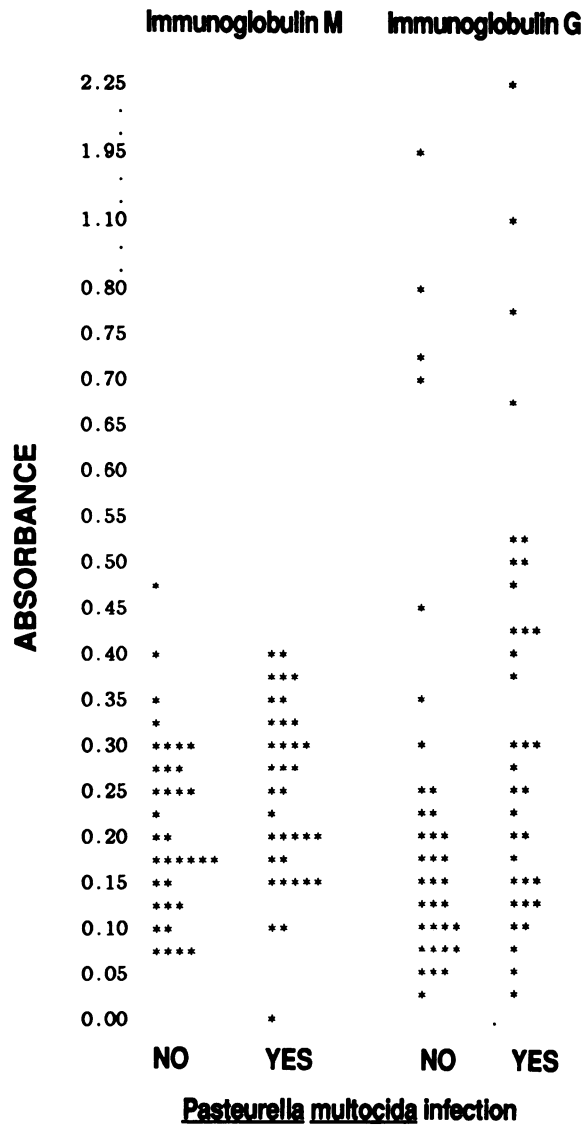

FIG. 1. Immunoglobulin levels in weanling rabbits with and without *P. multocida* infection.

(19) reported that infection with *P. multocida* increased from 4.3% in preweanlings to almost 100% in adults. DiGiacomo et al. (6) reported that infection with *P. multocida* increased from 4% in 12-week-old rabbits to 23% in 22-week-old rabbits and that 72% of adults had infection. Both *B. bronchiseptica* and *P. multocida* were shown to be common inhabitants of the nasal cavity of normal rabbits (8, 16). Although *P. multocida* has long been associated with disease in rabbits (27), *B. bronchiseptica* has been incriminated only as a result of experimental studies (25) in which rabbits were treated with cortisone and inoculated intranasally. The sites of localization of *P. multocida* and *B. bronchiseptica* in the respiratory tract may aid in understanding the development of disease in rabbits. The predilection of *B. bronchiseptica* for the trachea and bronchi (25) and of *P. multocida* for the nares, paranasal sinuses, and middle ears in adults (14, 19, 22, 25, 27) has been noted. *B. bronchiseptica* adheres preferentially to ciliated mucosal cells (18, 24) and thus resists respiratory clearance. Ciliostasis caused by *B. bronchiseptica* (2) may induce conditions suitable for adhesion by *P. multocida*, such as squamous metaplasia of mucosal cells (3, 12). This relationship could account for the greater number of infections with *P. multocida* only in older rabbits and the greater number of infections with *P. multocida* or *P. multocida* and *B. bronchiseptica* associated with disease. Also, dysfunctions of macrophages have been associated with colonization of the respiratory tract by *B. bronchiseptica* in rabbits (29). Various mechanisms of escape from the immune system have been suggested for *P. multocida* (13, 17, 21), permitting it to colonize mucosal cells in the presence of humoral antibody and competent neutrophils. Some serotypes of *P. multocida* were resistant to phagocytosis, while others were resistant to killing by neutrophils (1).

Atrophic rhinitis in rabbits was associated with *P. multocida* and concurrent *P. multocida* and *B. bronchiseptica* infections but not with *B. bronchiseptica* infection (5a). Isolates of *P. multocida* were serotype A:12. The turbinate atrophy in rabbits was similar to atrophic rhinitis in swine, which has been linked to combined *P. multocida* and *B. bronchiseptica* infections (23). However, persistent turbinate atrophy in pigs was induced by toxigenic *P. multocida* in the absence of *B. bronchiseptica* when the nasal mucosa was pretreated with dilute acetic acid (9). Purified toxin from swine *P. multocida* type D strains caused severe turbinate atrophy in pigs (7, 20). Using an enzyme-linked immunosorbent assay, Foged et al. (11) found that both type D and A

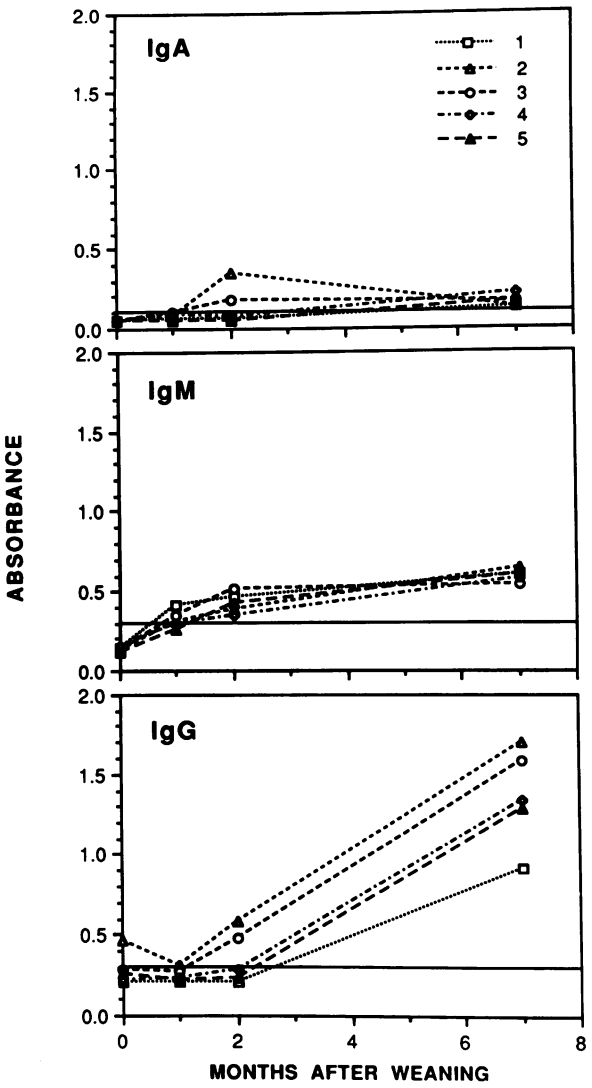

FIG. 2. Mean absorbance values of IgA, IgM, and IgG in female rabbits grouped by *P. multocida* infection: group 1, infection never detected; group 2, infected at weaning and throughout life; group 3, infection 1 month after weaning and throughout life; group 4, infection 2 months after weaning and throughout life; group 5, infection 1 to 2 months after weaning but not at necropsy. Solid line indicates threshold for a positive serologic response (IgA = 0.1; IgM and IgG = 0.3).

strains of *P. multocida* reacted with murine monoclonal antibodies with specificity for the toxin, which is a protein with a molecular weight of approximately 143,000. It will be of interest to determine whether toxin from serotype A:12 isolates is a factor in producing atrophic rhinitis and whether interacting virulence factors of *P. multocida* and *B. bronchiseptica* are necessary for the production of URD in rabbits.

In our study, no relationship was found between IgG levels and *P. multocida* infection in weanlings, suggesting that maternally derived antibodies offer no protection against *P. multocida* infection. Comparison of immunoglobulin levels in rabbits noninfected or transiently infected with *P. multocida* (groups 1 and 5) and persistently infected with *P. multocida* (groups 2, 3, and 4) revealed diminished IgA and early increased IgM responses in the former groups. IgG levels were highly correlated with infection. There was no relationship between humoral immunity and resistance to *P. multocida* infection.

Nakagawa et al. (19) also showed that serum antibodies, detected by tube agglutination, were strongly correlated with isolation of *P. multocida* from adults but not rabbits <2 months old. Among 47 rabbits 5 to 6 months old that were negative for *P. multocida* by nasal culture, Holmes et al. (14) detected 15 that were seropositive by enzyme immunoassay. At necropsy, *P. multocida* was recovered from the nasopharynx or middle ears of 14 rabbits. Thus, a test for IgG antibodies to *P. multocida* is useful for detecting occult *P. multocida* infections in young adult or adult rabbits even though transient infection with antibody production may occur. In our study, evaluation of rabbits 9 to 10 weeks old, 13 to 14 weeks old, and >6 months old revealed that 50, 51, and 83%, respectively, had nasal *P. multocida* infection, whereas 25, 44, and 95%, respectively, had IgG antibodies against *P. multocida*. Hence, acute infections were underdetected by serology and chronic infections were underdetected by cultural techniques. Clearly, detection of *P. multocida* infection in rabbits is best accomplished by a combination of deep nasal culture and serologic assay for IgG antibodies.

We concluded that the upper respiratory tract of rabbits is colonized by both *P. multocida* and *B. bronchiseptica*. While most rabbits are infected with *B. bronchiseptica* at an early age, the probability of infection with *P. multocida* increases with age. At any age, respiratory tract diseases are associated with *P. multocida* and not *B. bronchiseptica* infection. There is no evidence that either passively acquired antibodies (i.e., weanlings) or actively acquired antibodies (i.e., adults) provide protection against pasteurellosis.

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